Received: 4 May 2022 | Accepted: 12 May 2022

DOI: 10.1111/resp.14305

CONTEMPORARY CONCISE REVIEW

Official Journal of the Asian Pacific Society of Respirology
Respirology APSR WILEY

Contemporary Concise Review 2021: COVID-19 and other respiratory infections

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Funding information
Health and Medical Research Fund, Grant/Award Numbers: COVID1903003, COVID190126; Research Grants Council, University Grants Committee, Grant/Award Numbers: T11-712/19-N, T11-705/21-N; SH Ho Foundation

Handling Editor: Philip Bardin

Summary of key points

- Bats are likely the primary source of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- Minks are highly susceptible to infection by SARS-CoV-2.
- Transmission from asymptomatic individuals was estimated to account for over 50% of all transmissions of coronavirus disease 2019 (COVID-19) cases.
- SARS-CoV-2 is evolving towards more efficient aerosol transmission.
- Remdesivir, baricitinib, tocilizumab and dexamethasone are frequently used for the treatment of patients with respiratory failure due to COVID-19.
- There is a rising incidence of non-tuberculous Mycobacterium pulmonary disease globally, with a higher prevalence in Asian countries than in the Western world.
- Protracted bacterial bronchitis is a common cause of chronic productive cough in childhood.
- Re-emergence of respiratory syncytial virus may occur after the relaxation of infection control measures and the reopening of borders during COVID-19 pandemic.

KEYWORDS
antiviral, clinical, COVID-19, respiratory infections, review

INTRODUCTION

The coronavirus disease 2019 (COVID-19) started with a cluster of pneumonia of unknown cause in Wuhan, China, at the end of 2019.[1] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was rapidly identified as the culprit virus. The World Health Organization (WHO) declared COVID-19 a pandemic in March 2020. Two years after this announcement, there have been more than 5 hundred million confirmed cases of COVID-19, including 6 million deaths, reported to the WHO.[2] In this review, different aspects of COVID-19 with salient updates on other respiratory infections published mainly in 2021 are briefly reviewed.

COVID-19

Origin of SARS-CoV-2 and intermediary animal source

There is growing evidence for a bat origin of SARS-CoV-2 beyond China in Southeast Asia. Whole-genome sequences obtained from five bats (*Rhinolophus acuminatus*) in a cave in Thailand yielded one isolate (named RacCS203), which is mostly related to the RmYN02 isolate found in *Rhinolophus malayanus* in Yunnan, China. SARS-CoV-2 neutralizing antibodies were also detected in bats of the same colony and in a pangolin at a wildlife checkpoint in Southern Thailand. Antisera raised against the receptor-binding domain (RBD) of RmYN02 was found to cross-neutralize SARS-CoV-2, although the RBD of RacCS203 or RmYN02 failed to bind angiotensin-converting enzyme (ACE) 2 receptor.[3]

There were outbreaks of SARS-CoV-2 in mink farms in the Netherlands and Denmark in 2020. Some cats and dogs from infected farms tested positive for the virus, but rabbits, chickens and horses sampled on several farms, and wildlife sampled near the infected mink farms were negative for SARS-CoV-2. Minks are highly susceptible to infection by SARS-CoV-2, but the routes of transmission between farms are uncertain other than through direct human contact.[4]

Transmission and clinical presentation

SARS-CoV-2 transmits mainly by droplets which gain entry into the respiratory tract through the ACE2 receptor. The

level of ACE2 expression in the lower respiratory tract (LRT) is increased in elderly and males, but is not related to the pack-years smoked.[5] In a mouse model expressing human ACE2, high viral loads were detected in the lungs as early as 2 days post-infection, which reproduced the progression of COVID-19 in the LRT.[6] The distribution of ACE2 receptors in the body is one of the determining factors of predominant symptoms presented in COVID-19.[7]

In a decision analytical model of multiple scenarios of proportions of asymptomatic individuals with COVID-19 and infectious periods, transmission from asymptomatic individuals was estimated to account for over 50% of all transmissions.[8] A retrospective observational study in Wuhan has shown that children and adolescents were less susceptible to SARS-CoV-2 infection, but were more infectious than older individuals within households. Presymptomatic cases were more infectious while individuals with asymptomatic infection were less infectious than symptomatic cases.[9] The clinical spectrum of SARS-CoV-2 infection is summarized in Table 1.[10]

Compared with late presenters (presenting to hospital ≥7 days from symptom onset), early presenters of COVID-19 (<7 days from symptom onset) were older, more likely to have significant comorbidities (hypertension, thromboembolic and renal diseases) and less likely to report cardinal symptoms including fever, cough, dyspnoea and diarrhoea. Early presenters had less infiltrates on chest x-ray while the presence of infiltrates in this group revealed an increased risk of adverse outcomes.[11]

The duration of viral shedding may be prolonged in males, elderly, immunocompromised hosts, corticosteroid users and those with high fever, delayed hospitalization, severe or critical illnesses.[12,13] The factors that affect the clinical sensitivity or specificity of SARS-CoV-2 tests include days from symptom onset, sampling site and antigen test compared with reverse transcriptase-PCR testing.[14]

A study with air and environmental samplings has shown that SARS-CoV-2 is evolving towards more efficient aerosol transmission, and loose-fitting masks provide only modest source control. Therefore, social distancing measures and tight-fitting masks and respirators will be required until vaccination rates are very high.[15]

A British study has shown a higher hospitalization or emergency care attendance risk for patients with COVID-19 infected with the delta variant compared with the alpha variant,[16] while a matched controlled study in Sweden has shown COVID-19 as a risk factor for acute myocardial infarction and ischaemic stroke.[17] A prospective, multicentre cohort study in 302 UK healthcare facilities has shown that complications and worse functional outcomes in patients hospitalized with COVID-19 are high, even in young, previously healthy individuals. Acute complications are associated with reduced ability to self-care at discharge, with neurological complications being associated with the worst functional outcomes.[18]

A prospective, longitudinal study has shown that Long-COVID is associated with weak anti-SARS-CoV-2 antibody response, severity of illness and female gender. Late clinical events and persistent symptoms in the medium and long term occur in a significant proportion of patients hospitalized for COVID-19.[19] A population-based cohort study using the Danish prescription and health insurance registries has shown that the absolute risk of severe post-acute complications after SARS-CoV-2 infection not requiring hospitalization is low. Nevertheless, more frequent visits to general practitioners and hospital outpatient clinics could indicate COVID-19 sequelae.[20]

Autopsy findings and radiological features

A large multi-institutional autopsy survey has shown that patients dying of or with COVID-19 had an average of 8.9 pathological conditions documented at autopsy, with a combination of prior chronic diseases and acute conditions acquired during hospitalization. Clinical conditions during terminal hospitalization were cited 395 times for the 135 autopsied decedents and predominantly encompassed acute failure of multiple organs and/or impaired coagulation while myocarditis was rare.[21]

Kianzad et al. explored the relationship between the histopathological findings and the radiological patterns in eight autopsy cases, who had thorax computed tomography (CT) within 1–3 days before death. They found that the different typical CT patterns in COVID-19 were not related to specific histopathological patterns. Microvascular damage and thrombosis were even encountered in the radiologically normal lung.[22]

Neuroimaging has revealed that localized inflammation in intracranial olfactory structures and persistent olfactory impairment with or without perceptual distortions (i.e., parosmias or phantosmias) after SARS-CoV-2 infection could serve as a marker to identify people with an increased long-term risk of neurological disease (Figure 1).[23]

TABLE 1 Clinical spectrum of SARS-CoV-2 infection

- Asymptomatic or presymptomatic infection: Individuals who test positive for SARS-CoV-2 using a virologic test but who have no symptoms that are consistent with COVID-19.
- Mild illness: Individuals who have any of the various signs and symptoms of COVID-19 but who do not have shortness of breath, dyspnoea or abnormal chest imaging.
- Moderate illness: Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥ 94% on room air at sea level.
- Severe illness: Individuals who have SpO_2 < 94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mm Hg, respiratory rate > 30 breaths/min or lung infiltrates > 50%.
- Critical illness: Individuals who have respiratory failure, septic shock and/or multiple organ dysfunction.

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Source: NIH.[10]

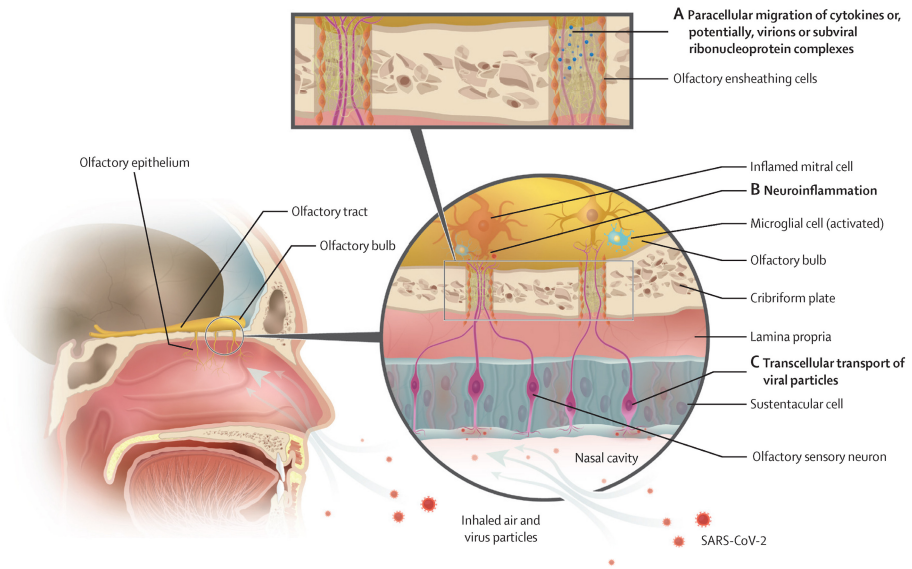

FIGURE 1 Potential pathways by which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can infect the olfactory bulbs and generate inflammation. (A) Paracellular migration; molecules or virions can be transported across the cribriform plate through intercellular gaps between the olfactory ensheathing cells or within empty nerve fascicles. (B) Sterile neuroinflammation; immunological response marked by proinflammatory mediators (i.e., cytokines and chemokines) that are activated by the virus, which has an initiating but secondary role. (C) The transcellular (trans-synaptic) transport pathway; virions could be transferred across the cribriform plate through anterograde synaptic transport. Reproduced from Xydakis et al.,[23] with permission.

TABLE 2 Risk factors for severe COVID-19

- Age older than 60 years (increasing with age).
- Underlying noncommunicable diseases: hypertension, diabetes mellitus, cardiac disease, chronic lung disease, cerebrovascular disease, mental disorders, chronic kidney disease, immunosuppression, HIV, dementia, obesity and cancer have been associated with higher mortality.
- Other risk factors associated with higher risk: smoking and higher sequential organ failure assessment (SOFA) score and D-dimer > 1 μg/L on admission were associated with higher mortality.
- In pregnancy, increasing maternal age, high BMI, non-White ethnicity, chronic conditions and pregnancy specific conditions such as gestational diabetes and pre-eclampsia.

Abbreviation: COVID-19, coronavirus disease 2019.
Source: WHO, 2021.[25]

Pulmonary embolism (PE) is a common complication, and systemic microangiopathy may cause profound vascular and perfusion abnormalities in the absence of PE, as found by dual-energy CT imaging. This may explain the out-of-proportion acute hypoxaemic respiratory failure in COVID-19 pneumonia.[24]

Risk factors for severe COVID-19

Various risk factors for severe COVID-19 have been described (Table 2).[25] Among these factors, increasing age is a strong predictor of in-hospital mortality.[25,26] Asthma, although a chronic respiratory illness, is not considered a risk factor for severe COVID-19.[27] The reduced ACE2 receptor expression in the LRT in asthma patients may be protective.[5] In addition, environmental factors may contribute. By using the 10-year particulate matter ≤2.5 μm ($PM_{2.5}$) exposure at the residential zip code, Mendy et al. found that long-term exposure to $PM_{2.5}$ was associated with increased hospitalization in COVID-19.[28] An et al. retrospectively analysed the association of inhaled corticosteroid (ICS) use with COVID-19 prognosis using the government health insurance system in South Korea, and revealed that the use of ICS was not associated with the hospital length of stay (LOS), intensive care unit (ICU) admission and all-cause mortality.[29] The development of secondary bacterial infection following COVID-19 was associated with persistent fever, increased oxygen requirements, shock, increased ventilatory and organ support and higher mortality.[30] Cytokine dysregulation has been proposed as the driver of inflammation. Among critically ill patients, monocyte chemoattractant protein-1 predicted the duration of mechanical ventilation, highest norepinephrine dose administered and length of ICU stay.[31]

Treatment

Numerous randomized controlled trials (RCTs) on both non-pharmacological and pharmacological options for COVID-19 targeting different disease severities have been conducted.

Respiratory and oxygen support

Hypoxaemic respiratory failure is common in severe COVID-19 pneumonia. During the COVID-19 outbreak, non-invasive respiratory support, including high-flow nasal cannula (HFNC), continuous positive airway pressure and non-invasive ventilation (NIV), is a feasible strategy to cope with the massive demand for ventilatory assistance outside the ICU.[32] In severe COVID-19 pneumonia, the choice between HFNC and NIV does not alter the subsequent need for intubation at 48 h.[33] A negative-pressure, well-ventilated room with at least 12 air exchanges per hour would be ideal to remove any infectious aerosols.[34]

Jones et al. identified spontaneously breathing patients who were indicated for proning (required supplemental oxygen or was tachypnoeic) in a retrospective analysis. The majority of these patients received supplemental oxygen via nasal prongs only. There was no evidence of reproducible response to proning and no relationship between the effect of proning on first treatment with subsequent treatments.[35] In a subsequent RCT involving 1126 patients who required respiratory support with HFNC for acute hypoxaemic respiratory failure due to COVID-19, it was found that awake prone positioning reduced the incidence of treatment failure and the need for intubation without any signal of harm.[36]

Pharmacological options

Pharmacological aspects can be further subdivided into early antiviral treatment and late immunomodulatory treatment,[37] which combats against the direct viral effect (high viral load)[38] and cytokine dysregulation (hyperinflammation causing further organ damage), respectively.[39]

Among recently exposed, asymptomatic individuals, both bamlanivimab/etesevimab or casirivimab/imdevimab combinations were effective post-exposure prophylaxis before the emergence of Omicron. These two combinations, both being neutralizing monoclonal antibodies that target the surface spike glycoprotein of SARS-CoV-2 which mediates viral entry into host cells, reduced the incidence of symptomatic COVID-19, with an absolute risk difference of −6.6% and −13.3%, respectively, when compared with placebo.[40] In non-hospitalized patients with mild to moderate COVID-19 and a high risk for progression to severe disease, both intravenous bamlanivimab/etesevimab and casirivimab/imdevimab within 3 days after a laboratory diagnosis of COVID-19 can reduce the incidence of COVID-19-related hospitalization and death from any cause (relative risk reduction: bamlanivimab/etesevimab 70%; casirivimab/imdevimab 2400 mg group 71.3%; casirivimab/imdevimab 1200 mg group 70.4%), and enhance the decline in viral load at day 7 before the emergence of Omicron.[41,42] However, these monoclonal antibodies are no longer distributed due to lack of efficacy against the Omicron.

In hospitalized COVID-19 patients with LRT involvement, remdesivir, a broad-spectrum anti-RNA virus nucleoside analogue originally designed for Middle East respiratory syndrome coronavirus and Ebola virus,[43] is the first antiviral agent endorsed and repurposed for COVID-19.

Dexamethasone, as an immunomodulatory agent, is indicated for moderate or severe COVID-19. In the RECOVERY trial, dexamethasone 6 mg daily up to 10 days resulted in lower 28-day mortality in patients who were receiving either invasive mechanical ventilation (IMV) or oxygen alone at randomization but not among those receiving no respiratory support.[44]

The other two effective immunomodulatory agents are tocilizumab (a monoclonal antibody against the IL-6 receptor to counteract the elevated IL-6 levels due to immune dysregulation and hyperinflammation) and baricitinib (a Janus kinase [JAK]) inhibitor targeting the cytokine storm. The use of tocilizumab in severe COVID-19 pneumonia has induced conflicting results in several landmark trials.[45,46] Two subsequent meta-analyses confirmed that the use of tocilizumab was associated with a reduction in mortality and with the need for IMV in hospitalized COVID-19 patients.[47,48] While for baricitinib, it reduces the recovery time and accelerates improvement in clinical status among patients with COVID-19, especially among those receiving high-flow oxygen or NIV,[49] and reduces mortality in those receiving IMV or extracorporeal membrane oxygenation.[50] A meta-analysis comprising 12 studies of 3564 patients concluded that baricitinib improved the mortality rate, ICU admission, the requirement for IMV and the oxygenation index.[51]

Azithromycin,[52] doxycycline[53] and colchicine[54] have been proven ineffective in hospitalized patients in improving overall mortality, initiation of ventilation and duration of hospital stay. High-titre convalescent plasma did not improve survival or other outcome in patients hospitalized with COVID-19,[55] but early administration appeared useful in reducing the progression of COVID-19 in mildly ill infected older adults.[56]

Vaccination

Vaccination, in addition to community-wide interventions such as mask-wearing and social distancing,[57] is pivotal in the battle against COVID-19. Standard vaccination of BNT162b2 (Pfizer-BioNTech), AZD1222 (Oxford AstraZeneca), mRNA-1273 (Moderna) and CoronaVac (Sinovac) all offer high vaccine effectiveness against the ancestral SARS-CoV-2 strain and the Delta variant.[58–62] However, the current challenges from the Omicron variant are the waning neutralizing antibody titres with time. The booster dose provides a solution to these problems by boosting the neutralizing antibody responses.[63]

The reasons for low vaccination uptake include vaccine hesitancy (vaccine safety and effectiveness concern), perceived scientific uncertainty, low disease risk perception, low trust in authorities and other stakeholders and global vaccine inequity (late acquisition of the vaccine in some developing countries).[64,65]

Impact and transformation of health care during COVID-19

Due to the highly contagious nature of SARS-CoV-2, violation of social distancing and infection preventive measures has led to sporadic outbreaks through clustering of people in different settings, including pubs, residential care homes for the elderly, cruises and religious places.[66]

Despite effective preventive measures, social distancing has changed the daily routine of each human and the

healthcare service in the world. Surveyed American and Australian adults would consider delaying or avoiding medical care due to concerns with the COVID-19 pandemic.[67] Cancer services are also delayed, with a significant projection of increased cancer death as the next wave of non-infective disease pandemic.[68] The stringent infection control around aerosol-generating procedure measures also delays the set-up of NIV services for patients with type 2 respiratory failure with a subsequent increase in mortality.[69] The mental health among healthcare workers is significant, with a higher prevalence of anxiety, depression and other mental illnesses than the general public in the COVID-19 pandemic. Consistent and accurate information, adequate resources and training, and physical and mental support should be proactively delivered by the governing bodies to relieve the mental stress of healthcare workers.[70]

The introduction of social restriction in New Zealand led to a significant reduction in the admission of acute infectious respiratory admissions, in parallel to the drop of circulating respiratory viruses.[71] Strong attention to infection control principles may limit the spread of antibiotic-resistant pathogens between patients, which may continue to benefit after the COVID-19 pandemic.[72] Telemedicine was rapidly adopted as a widespread model of healthcare delivery during the early COVID-19 pandemic, but it declined when the pandemic continued. Isautier and McCaffery stressed the importance of reflecting on patients' experiences and satisfaction with telehealth when building up and maintaining the telemedicine service. Appropriate platform and mode of healthcare delivery should be modified based on the patient's need.[73] While facing the difficulties of holding an in-person multidisciplinary meeting (MDM) for complex diseases such as interstitial lung disease and lung cancer, clinicians may convert the MDM to virtual format and benefit more patients through the online formation of a larger conglomerate of virtual MDMs.[68,74] The improved collaboration between respiratory physicians and intensivists with optimal critical care resource use could help reduce delay in discharge and patient LOS and increase ICU bed availability.[75]

OTHER RESPIRATORY INFECTIONS

MAC pulmonary disease

Recent epidemiology studies have revealed a rising incidence of non-tuberculous Mycobacterium pulmonary disease (NTM-PD) both regionally and globally, with a higher prevalence in Asian countries than the Western world.[76] The presence of comorbidities is a poor prognostic factor leading to a higher hospitalization and mortality rate.[77]

The latest treatment guideline endorses the use of amikacin liposome inhalation suspension (ALIS) in refractory *Mycobacterium avium* complex (MAC)-PD, which is defined as remaining sputum culture-positive after 6 months of guideline-based therapy (GBT). In the landmark CONVERT trial, the addition of ALIS to GBT in refractory MAC-PD achieved significantly greater culture conversion by month 6 than GBT alone and the therapeutic effect could sustain and remain durable 12 months after culture conversion.[78] Hearing loss and renal function abnormalities were generally similar between treatment arms in the CONVERT trial, except for more tinnitus in the ALIS arm. A subsequent open-label extension study identified no additional safety concerns.[79]

Asakura et al. found that serum Krebs von den Lungen-6 (KL-6) levels were significantly higher in MAC-PD patients than in healthy controls. The serum KL-6 level was significantly associated with disease progression, together with positive acid-fast bacilli and cavitary lesions. The change in serum KL-6 was significantly higher in the disease progression group; it decreased post-treatment, reflecting the negative sputum culture conversion. This may be a potential biomarker in the future.[80]

Protracted bacterial bronchitis

Protracted bacterial bronchitis (PBB) is a common cause of chronic productive cough in childhood. It is defined as a wet cough of at least 4-week duration with no identified specific cause of cough that resolved following 2–4 weeks of appropriate antibiotics.[81] Childcare attendance, prior history of chronic cough and age < 2 years increased the risk of PBB following the healthcare presentation for an acute cough illness in children, while a baseline diagnosis of asthma/reactive airways disease or bronchiolitis decreased the risk.[81] Clinicians and parents should be aware of the risk factors and symptoms for PBB. Such knowledge and health-seeking behaviour can be improved through education with culturally secure health information. Laird et al. have shown that the knowledge translation approach to improving recognition and management of chronic wet cough is feasible in Australian Aboriginal children.[82] PBB has impact on the development of subsequent airway diseases. A prospective single-centre study found that, after the post-index PBB episode, 67.5% had ongoing symptoms and 9.6% had bronchiectasis. Significant predictors of bronchiectasis were recurrent PBB in year 1 of follow-up and the presence of *Haemophilus influenzae* in the bronchoalveolar lavage. Clinician-diagnosed asthma at final follow-up was present in 27.1% of children with PBB. Positive allergen-specific IgE at baseline and bronchomalacia were significant predictors of asthma diagnosis.[83] *Moraxella catarrhalis* was the most common organism (52.4%) identified in a retrospective analysis of 903 children.[81] Ruffles et al. performed the first RCT to assess the duration of antibiotic treatment in children with chronic wet cough and suspected PBB, by comparing the clinical cure (cough resolution) by day 28 between 2 and 4 weeks of amoxicillin-clavulanate. By day 28, there was no significant difference in clinical cure between the two groups, but the time to next wet cough exacerbation was significantly longer in the 4-week group than in the 2-week group.[84]

Respiratory syncytial virus

Respiratory syncytial virus (RSV) is a major cause of LRT infection and hospitalization in infants. Nebulized ALX-0171, a novel trivalent nanobody with antiviral properties against RSV, has been studied on its effect in children hospitalized for RSV acute severe LRT infection. It was shown that this drug, at different doses, led to a shorter time in viral clearance, as measured by the quantifiable limit on plaque assay, but it was not translated into an improvement in clinical outcomes.[85] In an experimental study, Liu et al. assessed lung function, airway inflammation and immunohistopathology in BALB/c mice infected by influenza, rhinovirus and RSV. They identified IL-17A, the archetype T-helper cell 17 (Th17) cytokine, as the common pathogenic molecule regulating the disease induced by the three viruses, and they induced severe airway constriction and inflammation 2 days post-infection. The neutralization of IL-17A by monoclonal antibody led to a number of beneficial effects, including a substantial drop in endogenous production of IL-17A, attenuation of the increase in airway resistance induced by the viral infection, resolution of airway hyperresponsiveness and reduction in the airway infiltration of neutrophils and lymphocytes.[86] Although there was no effect on viral replication, targeting the IL-17A may represent a novel therapeutic pathway in viral lung infections.[87]

During the COVID-19 pandemic, the circulation of RSV, together with acute infectious respiratory admissions, has dropped due to the strict contact-restriction policy in New Zealand.[71] However, a re-emergence of RSV is noted after the relaxation of infection control measures and the reopening of borders.[88] Although co-infection with SARS-CoV-2 and RSV (and other respiratory viruses) is uncommon in the past 2 years,[88] proactive measures should be prepared for this possible combination in the future.

ACKNOWLEDGEMENTS

David S. C. Hui is supported by the Health and Medical Research Fund Commissioned Research on the Novel Coronavirus Disease (COVID-19), Hong Kong SAR (COVID1903003 and COVID190126), RGC theme-based research schemes (T11-712/19-N and T11-705/21-N) and SH Ho Foundation.

CONFLICT OF INTEREST

None declared.

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How to cite this article: Chan KKP, Hui DSC. Contemporary Concise Review 2021: COVID-19 and other respiratory infections. Respirology. 2022;27(8):661–8. https://doi.org/10.1111/resp.14305